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Fab Fragments of Digoxin-Specific Antibodies Used to Reverse Ventricular Fibrillation Induced by Digoxin Ingestion in a Child

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ABSTRACT. Digitalis poisoning is a rare problem in children, but it may be life threatening. A case of massive overdose of digoxin in a 2½-year-old boy that produced prolonged ventricular fibrillation refractory to conventional therapy is reported. After two hours the boy was given digoxin-specific Fab fragments of antibody in sufficient quantity to bind his estimated dose of 10 mg. By completion of the treatment minutes later, normal rhythm and circulation were restored. The serum free digoxin level before antibody administration was >100 ng/ml, and it rapidly fell to undetectable levels after antibody was given. Digoxin bound to the antibody had a clearance half-life of approximately 48 hours. The child had no apparent neurologic damage and his intellectual function was normal on discharge. He had a transient hematuria and a residual incomplete right bundle branch block. Administration of purified Fab fragments of digoxin-specific antibodies can be life saving in children with digitalis poisoning, and prolonged cardiopulmonary resuscitation in children is justified when the cause of cardiac arrest is potentially reversible. *Pediatrics* 70:468-471, 1982; *digitalis poisoning, Fab antibodies digoxin, ventricular fibrillation, cardiopulmonary resuscitation, cardiac arrest.*

turbances, and neurologic symptoms requiring only observation and general supportive care. We report a case of massive overdose of digoxin that produced prolonged ventricular fibrillation refractory to conventional therapy, with a dramatic response to administration of antidigoxin antibodies. This case supports the efficacy of these antibodies in patients with severe digoxin overdose, and further demonstrates that meticulous cardiopulmonary resuscitation (CPR), even over a period of hours, can permit return to normal function.

CASE PRESENTATION

A 2½-year-old boy weighing 12 kg was brought to the Wyler Hospital Emergency Room of The University of Chicago after the onset of lethargy and vomiting earlier in the day. Approximately six hours before arrival, the family had discovered the patient's grandfather's medicine bottles on the floor with pills scattered about. These included digoxin (0.25 mg), isosorbide dinitrate (5 mg), and propranolol (20 mg). By history and pill count, it was determined that approximately 10 mg of digoxin had been ingested. The propranolol bottle was full; whether any isosorbide tablets were consumed could not be determined.

At presentation the child was markedly somnolent. An electrocardiographic rhythm strip demonstrated atrioventricular junctional tachycardia alternating with slow junctional rhythm of 40 beats per minute. Shortly thereafter, the patient stiffened and collapsed with ventricular fibrillation (Fig 1). Intubation was performed and CPR was initiated. In spite of multiple medications (sodium bicarbonate [65 ml], lidocaine [32 mg], phenytoin [20 mg], and propranolol [0.65 mg]) and several attempts at

Digoxin is often involved in therapeutic or toxic overdoses.¹ It is a rare cause of poisoning in children, but may be life threatening. Most digoxin ingestions in the pediatric age group result merely in gastrointestinal complaints, mild conduction dis-

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cardioversion, he remained in ventricular fibrillation interrupted by brief periods of slow junctional rhythm. Isoproterenol and atropine failed to accelerate this bradycardia.

Serial arterial blood gas determinations consistently showed pH in the range of 7.31 to 7.45, a PO_2 greater than 100 torr and PCO_2 less than 38 torr. Electrolytes and calcium levels were normal. The serum potassium level was 5.5 mEq/liter, and this was the highest value of potassium obtained during the entire hospitalization. Because of the refractory nature of the arrhythmias to conventional therapy, a transvenous pacemaker was placed in the right ventricle in an unsuccessful attempt to provide a rapid paced rate to suppress the arrhythmia. Simultaneously, consent was obtained from a parent, a small test dose was given, and the administration of purified Fab fragments of sheep digoxin-specific Fab fragments was begun intravenously in a dose calculated to neutralize 10 mg of digoxin. Following another dose of propranolol (0.5 mg) and cardioversion, the child's heart could be captured by the pacemaker at a rate of 130/min, with return of palpable pulses. His extremities rapidly warmed and he sat up 35 minutes after the end of antibody administration. The total time that the patient remained in ventricular fibrillation was 2½ hours. Serum free digoxin level drawn prior to initiation of therapy (approximately six hours after ingestion) was reported as greater than 100 ng/ml.

The child was brought to the intensive care unit and remained intubated on pancuronium bromide overnight. Dexamethasone was used to minimize laryngeal edema after the traumatic intubation. His urine output remained above 2 ml/kg/hr; an ECG demonstrated junctional tachycardia with a right bundle branch block pattern (Fig 2). He was extubated 14 hours after admission. Mild inspiratory stridor was treated with oxygen and racemic epinephrine. Wheezing was later noted for which aminophylline and ultrasonic nebulizer treatments were used; no signs of congestive heart failure were noted. A urinalysis showed +3 occult blood and 5 to 10 RBC per high power field (HPF). His ECG now showed normal sinus rhythm with incomplete right bundle branch block.

On day 4, the upper airway obstruction acutely worsened and the patient began retaining CO_2 . At bronchoscopy a laryngeal web and much subglottic granulation tissue were found which necessitated tracheostomy. He subsequently did well and the tracheostomy was removed three weeks later. At the time of discharge results of developmental testing and neurologic exami-

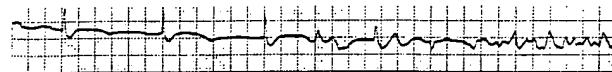


Fig 1. Rhythm record showing transition from slow aberrantly conducted rhythm to ventricular fibrillation in a 2½-year-old child shortly after arrival at emergency room.

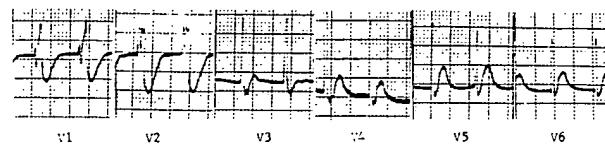
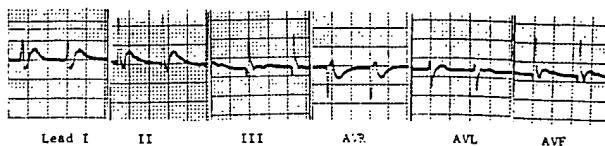


Fig 2. Standard 12-lead ECG obtained one hour after termination of ventricular fibrillation, showing rapid atrioventricular junctional rhythm with right bundle branch block.

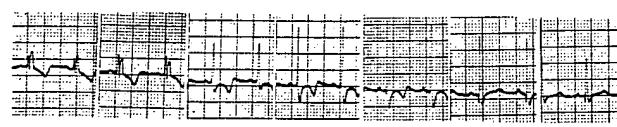
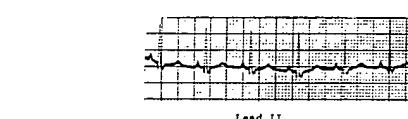
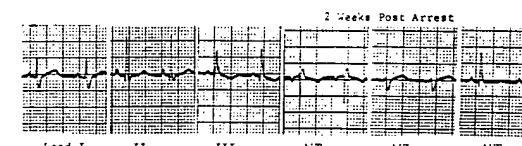


Fig 3. Standard ECG obtained two weeks after ventricular fibrillation and resuscitation, showing normal sinus rhythm with incomplete right bundle branch block.

nation were normal. His urinalysis remained abnormal with several red blood cells per high power field and a corrected creatinine clearance was only 21 ml/min. A persistent incomplete right bundle branch block pattern was noted in follow-up (Fig 3). The hematuria had resolved by eight weeks after discharge.

Multiple samples of blood were collected for determination of total (free plus Fab bound) and free digoxin levels. The serum free digoxin level fell precipitously from a prearrest value of greater than 100 ng/ml to undetectable levels after administration of digoxin-specific Fab fragments. The serum total digoxin (measuring both free and Fab-bound glycosides) peaked at 478 ng/ml at ten hours after antibody administration, decreased relatively rapidly to about 100 ng/ml, then steadily declined during the hospitalization in an exponential fashion with a half-time of approximately 48 hours (Fig 4).

DISCUSSION

Digitalis intoxication is a potentially serious medical event with mortality higher than 20% reported in some series.² Previously, the treatment of severe digitalis toxicity has been restricted to symptomatic

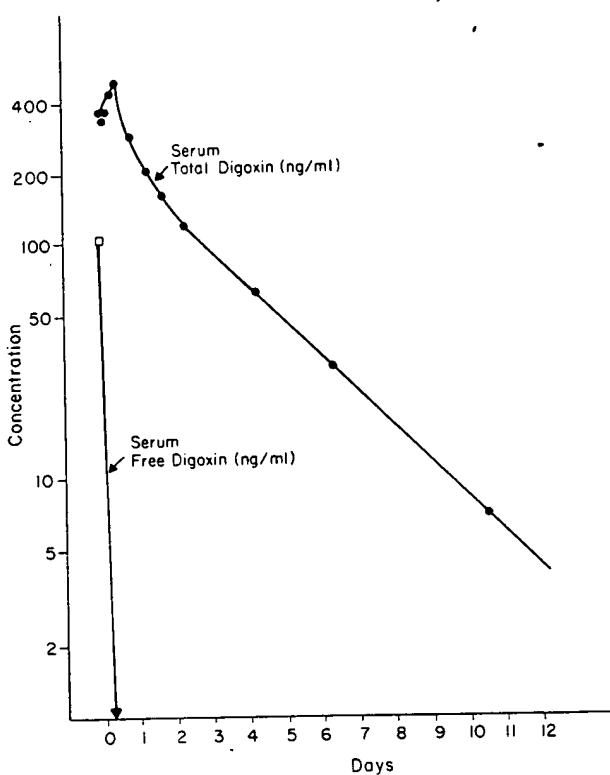


Fig 4. Response of serum digoxin concentration to administration of digoxin-specific Fab fragments. Serum free digoxin was greater than 100 ng/ml at time of admission and decreased to undetectable levels (<0.3 ng/ml) by one hour after antibody administration was complete. Serum total digoxin concentration (digoxin bound to antibody) increased to more than 400 ng/ml over the first 12 hours, and then fell rapidly. Note that scale of ordinate is logarithmic.

measures such as antiarrhythmic drugs and general supportive care.

In the early 1970s investigators began reporting the ability of antidigoxin antibodies to reverse the toxic effects of the glycoside in various experimental models.³⁻⁵ The intact antibody was found to be protective against digoxin toxicity. However, the intact antibody-digoxin complex was too large to enter the glomerular filtrate, resulting in prolonged elevation of plasma digoxin levels and raising concerns about the possibility of recurrent digoxin toxicity as the heterologous antibody population was degraded.⁶ In order to promote more rapid excretion of the digoxin-antibody complex, the 150,000 dalton antibody was enzymatically digested with papain to yield Fab fragments of smaller (50,000 dalton) size with intact binding affinity and specificity for digoxin.³ Digoxin-specific Fab fragments were then separated from nonspecific Fab fragments and Fc by affinity chromatography.³ The Fab fragment-digoxin complex is small enough to allow rapid clearance. The rapid complex clearance and absence of Fc fragment provide minimal antigenic stimulus to the patient.

Early studies showed reversal of digoxin-induced electrophysiologic toxicity by these antibodies; the antibodies removed both membrane-bound and extracellular digoxin by combining with free digoxin and shifting equilibrium in that direction.⁷ Animals given antibodies both before and after lethal doses of digoxin were protected from adverse effects.^{5,8,9}

In 1976, the first successful trial of purified digoxin-specific Fab in a human was made in a patient who developed intractable hyperkalemia and profound bradycardia after attempting suicide by massive digoxin ingestion.¹⁰ Sinus rhythm was restored within ten minutes after completion of Fab administration. It was found that the free serum concentration of digoxin (not bound to Fab) dropped rapidly to undetectable levels whereas total serum digoxin levels (presumably all bound to Fab) rose, consistent with the concept of dissociating the digoxin from its membrane site as stated above.

This is the 15th case of digoxin intoxication in which purified Fab fragments of digoxin-specific antibodies have been used in humans, and it is the first reported case in a child. The extraordinary nature of this case, with prolonged ventricular fibrillation and dramatic response to antibody therapy, underscores the practicality of this mode of therapy. It was further shown that prolonged resuscitative efforts are amply justified in the face of an acute and potentially reversible process.

Originally it was considered that the atrioventricular junctional tachycardia following the resuscitation might have been due to inadequate dosage of Fab fragments with residual digoxin toxicity. However, it is more likely that the initial cardiac hypoxia, resuscitative trauma, and pacemaker insertion caused both the transient junctional rhythm and the persistent dysfunction of the right bundle branch. The microscopic hematuria and low creatinine clearance level are suggestive of glomerular and/or renal tubular dysfunction, probably related, at least in part, to initial renal hypoxia and ischemia with resolution by several weeks after discharge. However, some glomerular damage from digoxin-antibody complexes cannot be excluded with certainty. Although further experience is needed to assure that administration of purified Fab fragments of digoxin-specific antibodies is safe in children, its use can be life saving. These fragments can be obtained for clinical treatment according to a Food and Drug Administration-approved protocol in several medical centers in the United States.

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Centers from Which Digoxin-Specific Fab Fragments May Be Obtained

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Arkansas, University of Arkansas for Medical Sciences, Little Rock, James E. Doherty, MD
California, University of California, Los Angeles School of Medicine, Los Angeles, Kenneth I. Shine, MD; University of California, San Francisco Medical Center, San Francisco, William W. Parmley, MD
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REFERENCES

- Smith TW, Haber, E: Digitalis (part IV). *N Engl J Med* 289:1125, 1973
- Beller GA, Smith TW, Abelmann WH, et al: Digitalis intoxication. *N Engl J Med* 287:989, 1971
- Curd J, Smith TW, Jaton JC, et al: The isolation of digoxin-specific antibody and its use in reversing the effects of digoxin. *Proc Natl Acad Sci USA* 68:2401, 1971
- Mandel WJ, Bigger JT Jr, Buttler VP Jr: The electrophysiologic effects of low and high digoxin concentrations on isolated mammalian cardiac tissue: Reversal by digoxin-specific antibody. *J Clin Invest* 51:1378, 1972
- Schmidt DH, Butler VP Jr: Reversal of digoxin toxicity with specific antibodies. *J Clin Invest* 50:1738, 1971
- Butler VP Jr, Schmidt DH, Smith TW, et al: Effects of sheep digoxin-specific antibodies and their Fab fragments on digoxin pharmacokinetics in dogs. *J Clin Invest* 59:345, 1977
- Watson JF, Butler VP Jr: Biologic activity of digoxin-specific antisera. *J Clin Invest* 51:638, 1972
- Schmidt DH, Butler VP Jr: Immunological protection against digoxin toxicity. *J Clin Invest* 50:866, 1971
- Hess T, Scholtysik G, Riesen W: The prevention and reversal of digoxin intoxication with specific antibodies. *Am Heart J* 96:486, 1978
- Smith TW, Haber E, Yeatman L, et al: Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. *N Engl J Med* 294:797, 1976

SLEEP DISRUPTIONS

Questionnaires about infant sleep patterns were sent by mail to a random sample of 1,158 families with 1 to 2 year olds. Returned questionnaires (67%) indicated that 20% of the children woke five or more times a week. Characteristics of 55 children with severe waking problems and their families were compared with 30 nonwaking control children. The wakers more commonly had other behavior and temperamental difficulties, irritability in the early months, and an adverse perinatal history. Their families had more stress and their mothers were more likely to have psychiatric symptoms. The role of various factors in the genesis and maintenance of sleep disruptions is discussed.

Submitted by Robert J. Haggerty, MD

Abstracted from Richman N: A community survey of characteristics of one- to two-year-olds with sleep disruptions (*J Am Acad Child Psychiatry* 20:281-291, 1981).